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Reply: Task- Versus Amphetamine-Induced Displacement of High-Affinity $D_{2/3}$ Receptor Ligands

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Task- Versus Amphetamine-Induced Displacement of High-Affinity $D_{2/3}$ Receptor Ligands

TO THE EDITOR: We have read with great interest a recent article by Ceccarini et al. (*1*). In their study, the authors evaluated the sensitivity of a single PET scan with the high-affinity dopamine $D_{2/3}$ receptor ligand ^{18}F-fallypride to reward-induced dopamine release. Ceccarini et al. concluded that striatal and extrastriatal dopamine release can be measured using a single ^{18}F-fallypride PET scan, if the timing and peak magnitude of the dopamine release are appropriate. Furthermore, their human PET and simulation experiments suggested that performance of a reward learning task during the scan, that is, during the interval in which radioligand binding occurs, induced displacement of the ligand in extrastriatal regions of the reward circuit, notably in the orbitofrontal cortex. These findings are generally in line with existing, albeit limited, literature on this theme; the report by Ceccarini et al. is of particular interest, being one of the first examining the dependence of competition on timing and magnitude of the endogenous dopamine release in the cerebral cortex.

The question of whether dopamine release can be captured in vivo is the theme of the well-established competition paradigm, notably on pharmacologic challenge with amphetamine. Indeed, amphetamine is a powerful releaser of dopamine, with a dose-dependent action that seems ideally suited to examine the sensitivity of radioligand binding to changes in endogenous dopamine concentration. Whereas amphetamine challenge evoked a reduction in ^{18}F-fallypride binding in striatum of anesthetized mice (*2*) and likewise in awake humans (*3*), the evidence is substantially less compelling for extrastriatal binding sites of ^{18}F-fallypride (*4*). Similarly, amphetamine challenge evoked only 5%–10% declines in the local cortical binding of the alternate high-affinity dopamine $D_{2/3}$ ligand ^{11}C-FLB 457 (*5*), whereas the same research group had earlier reported that a working memory task evoked widespread 10%–15% reductions in cortical binding of that ligand (*6*). In view of the well-known behavioral and physiologic effects of amphetamine, one might expect that amphetamine challenge should provoke a greater dopamine release than occurs during a cognitive task. Thus, it remains to be established how performing a cognitive task might evoke a greater or more prolonged decline in the availability of cortical dopamine $D_{2/3}$ receptors than can be evoked by amphetamine. This same reservation seems relevant to the observations of reward/learning-dependent ^{18}F-fallypride binding changes now reported by Ceccarini et al. Given that benzamide binding in living brain is influenced by changes in cerebral blood flow (*7*) and dependent on global perfusion (*8*), and in consideration that the blood oxygen level–dependent signal in orbitofrontal cortex is altered during reward processing (*9*), have the authors considered that their observations with ^{18}F-fallypride PET might be vulnerable to confounds arising from altered cerebral perfusion? We suggest that this consideration may call for systematic preclinical investigation of the effects of focally altered cerebral perfusion, as may occur during performance of cognitive tasks, on cortical ^{18}F-fallypride binding.

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REPLY: We read with interest the comments by Yakushev et al. regarding our article (*1*) examining the dependence of competition on the timing and magnitude of endogenous striatal and extrastriatal dopamine release using a single ^{18}F-fallypride PET recording and the linearized simplified reference region model (LSSRM) (*2*).

As they point out correctly, marked changes in regional cerebral blood flow (rCBF) can be a potential confounding factor in detecting neurotransmitter release (*3*). It could thus be hypothesized that the results reported in the in vivo reward task study as part of the article (*1*) may simply be due to a change in ^{18}F-fallypride

delivery or tissue efflux and not to competing dopamine release induced by a reward task.

We argue that in this single-injection protocol with the combination of the in vivo kinetics of ^{18}F-fallypride and the LSSRM approach, it is unlikely that rCBF-related changes would add major perturbations in ligand displacement, also under task paradigm conditions, as was also already stipulated by other simulation studies (*2,4*).

Although the LSSRM has several advantages by virtue of its requiring only single-day scanning and a single synthesis and administration of the radiochemical, and consequently avoiding session effects, practical implementation of the model implies that possible time-dependent alterations in rCBF are not fully accounted for. Briefly, as described in Equation 2 in the supplemental material of our article (*1*), the LSSRM can account for changes in perfusion via the β-parameter. Implementation of the full model is best suited for estimation of 4 parameters at a time. Attempts to estimate more than 4 parameters would result in a large covariance between the time-dependent parameters (α, β, and γ), translating into unreliable estimates. Therefore, parameters were customarily estimated by fixing $\alpha = \beta = 0$ and estimating the other 4 parameters (R, k_2, k_{2a}, and γ). This has indeed the potential of biasing the γ-estimate (i.e., ^{18}F-fallypride displacement).

Previous simulation studies have investigated the effects of transient increased ligand displacement and increased rCBF—considering possibilities such as proportional increase in transport (K_1) and clearance rate (k_2) so that the distribution volume remained constant—and separate increases in K_1 and k_2 (*4*). In the case of simultaneous increases, the changes in the PET binding curves are negligible. Increasing K_1 results in an increased tracer uptake with negative γ-estimates. On the other hand, an increase of 10% in k_2 results in significant positive γ-parameters. Therefore, the only possible confounding circumstance causing a positive measurement of γ due to blood flow alterations is an exclusive increase in k_2. If the permeability/surface product is assumed constant, a 10% increase in K_1 corresponds to a blood flow increase of approximately 30% for a typical flow rate of 0.5 mL/(g·min) (*5*). Assuming that the nondisplaceable binding is unaffected by the activation condition, a 10% increase in k_2 would also correspond to a 30% blood flow increase. This magnitude of blood flow increase, however, is not within the expected range during performance of a reward task. Activation perfusion studies with ^{15}O-H_2O and functional MRI have shown that the increase in orbitofrontal rCBF during performance of a monetary reward task is on the order of few percentage points (*6–8*). Nevertheless, simulations of the activation state have demonstrated that the LSSRM fits the data well even when rCBF-related effects were on the order of 20% (*2*). This rCBF-related issue was also addressed by Slifstein et al. (*5*), suggesting that artifactual rCBF-induced changes in measured radioligand binding are minor for ^{18}F-fallypride.

In addition, the recent findings of Cumming et al. (*9*) gave preliminary evidence that individual differences in global perfusion (using an image-derived surrogate of mean global cerebral blood flow) may bias the estimation of ^{18}F-fallypride nondisplaceable binding potential in the striatum but not in low-binding regions (i.e., thalamus and the inferior temporal lobe). Therefore, although rCBF may be a factor influencing the estimation of ^{18}F-fallypride nondisplaceable binding potential in regions with high receptor concentrations (i.e., striatal regions), this influence should be less important in low-binding regions (i.e., extrastriatal regions), where changes were observed in the monetary reward task study.

We therefore are confident that our observations with ^{18}F-fallypride and LSSRM are not artifacts of non–receptor-related effects such as altered cerebral perfusion and that the increased radioligand washout k_{2a} in response to reward-induced stimulation actually reflects reduced nondisplaceable binding potential detecting the presence of endogenous dopamine neurotransmission.

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